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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,784	12/13/2004	Gideon Gross	GROSS32	4624

1444 7590 06/29/2007

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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
06/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,784	GROSS ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed July 18, 2005, is acknowledged and has been entered.

Claims 9, 11, 14, 16, 17, 20, 23, 29, 30, 37, 38, 39, 41, 47, 48, 49, 52 have been amended. Claims 53-55 have been newly added.

2. Claims 1-55 are pending in the application and are under examination.

Information Disclosure Statement

3. The references cited in the information disclosure statement filed on July 10, 2006, have been considered.

Specification

4. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is GenBank™ (see, e.g., page 38).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

b. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such impermissible disclosures appear in the specification at, for example, page 18.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

c. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

Claims 1-55 are directed to a genus of structurally and functionally diverse polynucleotides, expression vectors comprising said polynucleotides, antigen-presenting cells comprising said polynucleotides, vaccines comprising said polynucleotides and methods of using said products to prevent or treat diseases, such as cancer or infection, wherein said polynucleotides encode polypeptides comprising a β2-microglobulin polypeptide linked through its carboxy terminus to a genus of structurally and functionally diverse "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" and through its amino terminus to a genus of structurally and functionally diverse "peptides comprising at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is not related to an autoimmune disease".

However, as will be explained in further detail in the following paragraphs, the specification only adequately describes "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane", wherein the polypeptide comprises the transmembrane and cytoplasmic domain from the MHC class I heavy chain of HLA-A2 which has the amino acid sequence of SEQ ID NO:2 or wherein the polypeptide comprises the transmembrane and cytoplasmic domain of the human CD3 ζ polypeptide. Furthermore, the specification does not adequately describe the genus of "peptides comprising at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is not related to an autoimmune disease" and only adequately describes antigenic peptides comprising a MHC class I epitope, wherein the peptide has a defined amino acid sequence in the specification (see for example pages

15-17 that discloses SEQ ID NOS giving the amino acid sequence of known MHC class I epitopes).

Notably, the specification discloses at page 13 that "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" include signal transduction elements capable of activating T cells or antigen-presenting cells. Then at page 14, the specification discloses that representative signal transduction elements include Fc receptor polypeptides.

In this case, the specification does not describe with any particularity the identifying structural and/or functional features of the genus of "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane". Notably, the specification, does not describe the structure of a sufficient number of species of the genus of "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane", to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. For example, the specification only provides evidence that the transmembrane and cytoplasmic domains from the MHC class I heavy chain of HLA-A2 or from the human CD3 ζ polypeptide have the requisite function of providing anchorage of β2-microglobulin to the cell membrane that is sufficient to generate antigen specific CTLs. Furthermore, the specification provides no correlation of the structure of these polypeptides with their ability to provide anchorage of β2-microglobulin to the cell membrane that is sufficient to generate antigen specific CTLs and therefore one of skill in the art would not be able to immediately envision which other "polypeptides" would have the requisite function.

For example, it is established in the art that there is a high degree of unpredictability in assigning particular structures or functions to a protein based on sequence homology alone because a protein's structure is dependent on its given amino acid sequence and cannot be determined *a priori* and the function of a given protein is also highly unpredictable and variable and cannot necessarily be linked to a given structure. For example, Skolnick et al. (*Trends in Biotechnology*, **18**: 34-39, 2000), discloses that the skilled artisan is well aware that assigning functional activities for any

particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Furthermore, as evidenced by Jones (Pharmacogenomics Journal, 1:126-134, 2001), protein structure "prediction models are still not capable of producing accurate models in the vast majority of cases" (page 133, 3rd paragraph). Finally, Tosatto et al state, "the link between structure and function is still an open question and a matter of debate" (Current Pharmaceutical Design, 12:2067-2086, 2006, page 2075, 1st new paragraph). Therefore, the structure and function of the genera of "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" is highly unpredictable and one of skill in the art would not immediately envision which polypeptides would have the requisite functions. Notably, since the genus of "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" is not adequately described the claimed products and methods are not adequately described.

Additionally, the specification discloses that "antigenic peptides comprising a MHC class I epitope that are not related to an autoimmune disease" include, for example, MHC class I epitopes from alpha-fetoprotein (see page 15) or MHC class I epitopes from the HIV envelope protein Tat. Notably, the specification is silent as to what diseases are considered autoimmune diseases and therefore one of skill in the art would not be able to immediately envision or recognize which antigenic peptides comprising MHC class I epitopes are not related to autoimmune diseases because as evidenced by Skolnick et al, Jones and Tosatto et al (supra) one of skill in the art would not be able to predict whether an antigenic peptide was related to an autoimmune disease given just its amino acid sequence.

Furthermore, one of skill in the art would not be able to recognize the species encompassed by the genus of antigenic peptides to which the claims are directed,

because multiple species included in this genus, and more particularly specifically recited in the claims, and are in fact related to autoimmune diseases. For example, Liu et al (Rheum. Int. 27:489-491, 2007) teach that the polypeptide alpha-fetoprotein is expressed in some cases of autoimmune hepatitis (see entire document, e.g., abstract). Furthermore, Kim et al (Mol. Biotech., 30:221-229, 2005) teach that a peptide from the HIV Tat polypeptide can suppress autoimmune diabetes (see entire document, e.g., abstract). Therefore, since polypeptides comprising these MHC class I epitopes are also know to be related to autoimmune diseases, one of skill in the art would not be able to immediately envision which MHC class I epitope was in the genus and which was not and, therefore, would not consider the applicant to be in possession of the claimed genus. Furthermore, the specification provides no evidence that one of skill in the art would be able to immediately envision or recognize which MHC class I epitopes are related to autoimmune diseases and which are not. Notably, since the genus of "antigenic peptides comprising a MHC class I epitope that are not related to an autoimmune disease" are not adequately described the claimed products and methods are not adequately described.

Thus, one of skill in the art would not consider the particularly described transmembrane and cytoplasmic domains from the MHC class I heavy chain of HLA-A2 polypeptide or from the human CD3 ζ polypeptide or the defined sequences of peptides comprising MHC class I epitopes as representative of their respective genera as the Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus.

Finally, it is noted that the specification has not adequately described DNA vaccines, cellular vaccines or pharmaceutical compositions comprising said polynucleotides for the prevention and treatment of cancer or diseases caused by pathogenic organisms, nor has it adequately described the methods of immunizing mammals to treat or prevent cancer or diseases caused by pathogenic organisms. Notably, the specification only provides evidence that antigen specific CTLs can be generated with a construct comprising as a MHC class I epitope amino acids 257-264 of

chicken ovalbumin (see figure 9 and description of figure 9 on page 10) and therefore does not provide any evidence that Applicant was in possession of using the claimed polynucleotides directed to tumor antigens or pathogenic organism antigens as a DNA vaccination, a cellular vaccination or any pharmaceutical composition for the prevention and treatment of cancer or diseases caused by pathogenic organisms. Notably, one of skill in the art would not consider the ability of a construct to generate antigen specific CTLs as representative of the constructs' ability to be a DNA vaccine, cellular vaccine or pharmaceutical composition for the prevention and treatment of cancer or diseases caused by pathogenic organisms.

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Although the skilled artisan could potentially screen for transmembrane and cytoplasmic domains that would have the requisite functions, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

It is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural

term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, having the ability to anchor β2-microglubulubin to the cell membrane does not distinguish the claimed "polypeptide stretch", from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Again, the genera of "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" and "peptides comprising at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is not related to an autoimmune disease", respectively all do not share common structural features that relate to their stated functions.

Given the lack of particularity with which the claimed polynucleotides, expression vectors comprising said polynucleotides, antigen-presenting cells comprising said polynucleotides, vaccines comprising said polynucleotides and methods of using said products to prevent or treat diseases, such as cancer or infection, wherein said polynucleotides encode polypeptides comprising a β2-microglobulin polypeptide linked through is carboxy terminus to a genus of structurally and functionally diverse "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" and through its amino terminus to a genus of structurally and functionally diverse "peptides comprising at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is not related to an autoimmune disease", are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members this genus, to which the claims are directed; and therefore the specification would not reasonably convey to the

skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

7. Claims 1-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claims are drawn to polynucleotides, expression vectors comprising said polynucleotides, antigen-presenting cells comprising said polynucleotides, vaccines comprising said polynucleotides and methods of using said products to *prevent or treat* diseases, such as cancer or infection, wherein said polynucleotides encode polypeptides comprising a β2-microglobulin polypeptide linked through is carboxy terminus to a genus of structurally and functionally diverse "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" and through its amino terminus to a genus of structurally and functionally diverse "peptides comprising at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is not related to an autoimmune disease".

As a first point, insofar as the products and methods are drawn to polynucleotides that one of skill in the art would not be able to immediately envision as set forth in the above rejection of the claims as lacking adequate written description rejection, one of skill in the art would be subject to undue experimentation to make polynucleotides commensurate in scope with the claimed invention. Notably, the specification lacks any specific non-general guidance on how to predict which transmembrane anchors will have the requisite function and how to predict which peptides are antigenic MHC class I epitopes that are not related to an autoimmune disease.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Furthermore, starting at page 23, the specification discloses the following:

> In one embodiment, there is provided a DNA vaccine for prevention or treatment of cancer comprising a polynucleotide that encodes a polypeptide comprising at least one antigenic determinant of at least one TAA.
>
> In another embodiment, there is provided a DNA vaccine for prevention or treatment of a disease caused by a pathogenic organism comprising a polynucleotide that encodes a polypeptide comprising at least one antigenic determinant of at least one pathogenic antigen.
>
> ...
>
> In one embodiment, the DNA vaccine is a naked DNA vaccine. It may contain a plasmid DNA that contains the polynucleotide of the invention controlled by a cytomegalovirus (CMV)

promoter. When the plasmid is introduced into mammalian cells, cell machinery transcribes and translates the gene. The expressed protein (immunogen) is then presented to the immune system where it can elicit an immune response. One method of introducing DNA into cells is by using a gene gun. This method of vaccination involves using pressurized helium gas to accelerate DNA-coated gold beads into the skin of the vaccine.

Therefore, the claims are reasonably interpreted to encompass the use of the claimed polynucleotides and expression vectors as DNA vaccines to prevent or treat diseases as well as the other claimed uses of the polynucleotides in cellular vaccines or pharmaceutical compositions to prevent or treat diseases or immunize a mammal.

However, as will be explained in further detail below, the specification does not enable the use of the claimed products in any form for the prevention or treatment of any disease. Notably, the specification only provides evidence that antigen specific CTLs can be generated with a construct comprising as an MHC class I epitope amino acids 257-264 of chicken ovalbumin (see figure 9 and description of figure 9 on page 10) and therefore one of skill in the art would be subject to undue and unreasonable experimentation to use the claimed products in methods of preventing and treating diseases. Therefore, since the specification provides no working examples wherein the claimed products prevent or treat any disease and merely provides prophetic examples that only give general guidance as to how to use the claimed product to prevent or treat diseases on pages 23-31, the specification is not deemed sufficient to enable the claims. Notably, at the time the instant application was filed, the state of the art indicated that DNA and cellular vaccines for the prevention and treatment of diseases was highly unpredictable in the art.

Notably, to address whether the products are useful for *preventing diseases* such as cancer or infections, it is noted that preventing cancer or infection is intractable, if not impossible; yet the specification provides no factual evidence suggesting that the claimed invention can be used to prevent cancer or infection in any animal. For example, to prevent an infection the claimed products would have to prevent the bacteria or virus from entering the host and as the products are directed to generating antigen specific CTLs that would only function after the bacteria or virus has entered the

host the products could not prevent infection. Moreover, even today it is established in the art that preventing cancer with a cancer vaccine is highly unpredictable. Very recently Lollini et al. (*Curr. Cancer Drug Targets.* 2005 May; **5** (3): 221-228) disclosed a complete prevention of mammary carcinoma was obtained in transgenic mice predisposed to this cancer by immunization with the so-called "triplex vaccine"; see entire document (e.g., the abstract). Even so, Lollini et al. teaches, "[m]ost current tumor antigens appear to be unsuitable targets for cancer immunoprevention" (abstract), since most are not have "crucial pathogenetic role in tumor growth" and/or are ineffective to stimulate both arms of the immune system (e.g., abstract). Lollini et al. (*Trends Immunol.* 2003 Feb; **24** (2): 62-66) explains although medicine in the postgenomic era offers an increasing possibility of detecting healthy individuals at risk of developing cancer who could benefit from tumor preventive vaccination, the identification of tumor antigens suitable for inclusion in such vaccines should require the tumor antigen have a crucial pathogenetic role for tumor growth to avoid the selection of antigen-loss variants (abstract).

In the alternative, the claims are directed to products that are useful for *treating* diseases including cancer and infection; yet, the specification provides no factual evidence suggesting that the claimed invention can be used to *treat* such diseases in any animal as it only provides evidence that antigen specific CTLs are generated towards chicken ovalbumin and does not provide any evidence that the tumor antigens or pathogenic antigens would create antigen specific CTLs sufficient to treat patients. More particularly, the specification does not include a disclosure of a determination of any therapeutically relevant, indicative endpoints, which might support the assertion of its usefulness, such as tumor regression or decrease in viral load, for example. The mere disclosure that antigen specific CTLs may be generated, does not constitute reasonable correlative evidence establishing the usefulness of the claimed invention in treating diseases.

To elaborate on this with specific examples relating to cancer, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; **1** (2): 277-290) teaches the "melanoma model" is the paradigm for studies of the effectiveness of T-cell-directed cancer vaccines; see entire document

(e.g., the abstract). Wang et al. teaches, "the success of these approaches has been limited [save for scattered reports] and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunisation can be induced but it is not sufficient, in most cases, to induce tumour regression" (abstract). In order to explain the lack of clinical success, despite the promise of preclinical data, Wang et al. teaches, among other reasons, clinical data suggest the possibility of a dissociation between immune responses detected in peripheral blood *versus* tumor, which suggests that is more important to determine immune response at the tumor site, rather than in the peripheral blood, in assessing the likely effectiveness of the treatment (page 281, column 1). Regardless of the cause for such poor extrapolation of preclinical findings, Wang et al. discloses the difficulty of correlating laboratory findings with clinical outcome is a significant obstacle to the assessment of the role of immune escape and/or tolerance in cancer progression (page 282, column 2). Furthermore, Wang et al. teaches, "[t]he published experience using the ELISPOT [assay] to monitor T-cell responses to cancer antigens is still limited" (page 283, column 2); and Wang et al. teaches the same is true of the "tetramer" assay (page 284, column 2). Wang et al. teaches, "there are no universally accepted correlates at this time between any method of in vitro immune monitoring and clinical outcome" (page 285, column 1).

Thus, due in part to the inadequacy of the methods used to assess the immune response mustered upon vaccination and the poor correlation of such results and clinically relevant endpoints, such as tumor regression, the art of cancer immunotherapy is highly unpredictable. Bodey et al. (*Anticancer Research.* 2000; **20**: 2665-2676) teaches, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey et al. comments, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). Thus, little has changed to alter the artisans' expectations of the still prospective immunotherapy since the invention was made. Cox et al. (*Science.* 1994; **264**: 716-719) teaches, "neither adoptive transfer of melanoma-specific CTLs nor

specific active immunotherapy with whole melanoma cells or cell-derived preparations has led to the eradication of melanoma in more than a minority of patients" (page 716, column 2). Then again, even that small note of promise has since faded. Bodey et al. discloses, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (page 2668, column 2). In the abstract Bodey et al. speculates upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research.* 1995; **7**: 46-49) states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). Published more recently, Bodey et al. (*supra*) states, "there should be caution about assuming that a single epitope or even a few epitopes combined will be as effective 'crude' materials, which might better be thought of as 'polyvalent'" (page 2668, column 2). Spitler (*Cancer Biotherapy.* 1995; **10**: 1-3) recognizes the lack of predictability of the nature of the art when she states, "ask

practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Whatever avenue the artisan takes, in view of the unpredictability in the art, the rarity and lack of uniformity in the successful application, and the numerous and substantial limitations encountered, the threshold of enablement is high. The specification must enable one of skill in the art to make and to use the invention with a reasonable expectation of success. To have success, the use of the invention must elicit a CTL response against the antigen that is sufficient to treat the disease. Boon (*Advances in Cancer Research.* 1992; **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have already occurred in the patient and in such cases, active specific immunization will be fruitless, since anergic CTL cannot be activated, will not proliferate, and are deficient in effector function. Several lines of evidence suggest that large tumor burdens can tolerize, or at least depress the capability to respond against the tumor (page 206, paragraph 2). Furthermore, among other mechanisms, Arceci (*Journal of Molecular Medicine.* 1998; **76**: 80-93) teaches, "it has been hypothesized that tumor cells may escape immune recognition and subsequent killing by failing to satisfy one or more of the [...] requirements for T cell antigen recognition and activation. For example, if antigen presentation does not occur because of low or absent expression of MHC or lack of a recognizable tumor antigen, then tumor cells would not be recognized" (page 83, column 2). Areci continues, "on the other hand, if antigen recognition occurs by T cells but tumor cells do not express a costimulatory molecule, then T cells might become anergic to the tumor cells" (page 83, column 2). Notably, Areci teaches, "most solid tumors usually do not express costimulatory molecules" (page 84, column 1); therefore, it is unlikely that the invention can be used to effectively immunize a patient against most cancers.

Furthermore, there is considerable art indicating that vaccines are ineffective,

even if antigen-specific T-lymphocytes can be activated by immunization protocols. For example, Wang et al (Sem. Immun. 27:105-117, 2005), teach that it is naïve to expect "that CTL induction is sufficient for an effective immune response" (see abstract). Furthermore, Lee et al. (*Journal of Immunology.* 1999; **163**: 6292-6300) teaches, "although comparative ex vivo sensitization of pre- and postvaccination PBMC [peripheral blood mononuclear cells, such as B- and T-lymphocytes] has identified reproducible, vaccine-specific systemic T cell responses to immunization, in the majority of cases no regression is seen" (page 6292, column 1). Additionally, Lee et al. teaches that melanoma antigen epitopes were identified and that these peptide epitopes were capable of inducing highly specific T cell responses against autologous and some HLA-matched tumor cells. Lee, et al disclose that "these studies gave the impression that vaccines induce powerful immunizations comparable to those demonstrable against common pathogens such as the influenza virus to which individuals are repeatedly exposed throughout their lifetime". However, "in most cases, this **vaccine-induced T cell reactivity still does not lead to tumor regression**" (emphasis added) (page 6299, column 1). One of the reasons for the discrepancy, Lee et al. suggests, may be that in vitro methods, which are commonly used to assess immune post-vaccination immune response, such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Lee et al. catalogs a variety of possible explanations for the lack of efficacy, including clonal deletion, exhaustion, or senescence, which are implicated in the development of systemic, epitope-specific immune tolerance, and inadequate immune response attributable to decreased T cell receptor signaling capacity or circulating immune-suppressive cytokines, but conclude that their data suggest that the extent rather than the quality of the response might be more significant limitation of the vaccination protocol (page 6299, column 2). More specifically, Lee et al. reports, "we were surprised at the relatively low numbers of CTL precursors after vaccination even in patients' samples that boasted an exceptional epitope-specific expansion in vitro" (page 6299, column 2). Lee, et al summarize their study, teaching that "a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the

PBMC of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma" (abstract). While Lee et al. refers specifically to the treatment of melanoma using a different epitope, the teachings are highly germane to the enablement issues relevant in the instant application, because the severe limitations will undoubtedly be shared by any protocol that uses the claimed invention, and there is no exemplification in the specification that would suggest otherwise.

In yet another example, Zaks et al. (*Cancer Research.* 1998; **58**: 4902-4908) teaches that immunization of patients diagnosed with cancer with a peptide epitope derived from the tumor antigen HER-2/neu/ErbB2 leads to activation of peptide-specific cytotoxic T-lymphocytes, but that the T-lymphocytes fail to recognize tumor cells that express the antigen. Zaks et al. discloses their experience is not unique (page 4907, column 2). Gao et al. (*Journal of Immunotherapy.* 2000; **23**: 643-653) discloses the finding that, although antitumor CTL response was enhanced by immunization, the tumors failed to regress. Gao et al. teaches that the observed lack of regression was associated with a lack of CTL migration to the tumor sites (abstract). Thus, activation of peptide epitope-specific CTL *is not an appropriate endpoint* and a prediction or estimation of efficacy based only upon such data is imprudent or inexact.

Notably, of particular importance, Margalit et al (J. Immun., 176:217-224, 2006) teach injecting a mouse model with a cellular vaccine comprising cells presenting a polypeptide comprising β2-microglubilin linked to the h-2K anchor and the MHC class I epitope comprising amino acids 181-188 TRP-2 which is encoded by a polynucleotide encompassed by the claims and that this vaccine *fails* to suppress the growth of established tumors (see entire document, e.g., page 219, figure 1 and page 222, left column). Moreover, many attempts to provide efficacious therapeutic or prophylactic immunotherapy for cancer patients have paradoxically failed; despite evidence that vaccination has induced proliferation of tumor antigen-specific CTL, no major protective antitumor response was seen over and over again in these cases. See, for example, Hu et al. (*Cancer Research.* 1996; **56**: 2479-2483); Jaeger et al. (*International Journal of Cancer.* 1996; **66**: 162-169); Mukherji et al. (*Proceedings of the National Academy of*

Science USA. 1995; **92**: 8078-8082); and for review, see Bocchia et al. (*Haematologica*. 2000; **85**; 1172-1206).

In view of the lack of the predictability of the art to which the invention pertains, the lack of established clinical protocols for effective treatment of diseases using said products, undue experimentation would be required to use the claimed products. Absent a specific and detailed description in applicant's specification of how to effectively practice the claimed products as naked DNA vaccines and absent working examples providing evidence which is reasonably predictive that the claimed products are effective for vaccinating individuals against cancer and pathogenic organisms, commensurate in scope with the claimed invention, one of skill in the art would be subject to undue experimentation without reasonable expectation of success to use the claimed products in a vaccine.

Conclusion

8. No claim is allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Gross et al (WO 01/91698, 2001) teach polynucleotides that encode polypeptides comprising a β2-microglobulin polypeptide linked through its carboxy terminus to polypeptide stretch that allow the anchorage of β2-microglobulin to the cell membrane and through its amino terminus to at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is related to an autoimmune disease.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached at Monday through Friday from 7:00 AM to 4:30 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-

0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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Respectfully,
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June 22, 2007